REMARKS

The Applicants would like to thank the Examiner for time taken on November 22, 2004 to discuss outstanding rejections in the application.

I. The Subject Matter of the Claims

In general, the subject matter of the claims relates to monoclonal antibodies specifically reactive with α_d integrin which also modulate TNFα activity.

II. The Objections to the Specification

Applicants have updated the priority claim as requested by the Examiner in paragraph three of the Action. Applicants maintain the priority claim to USSN 08/605,672, filed Feb. 2, 1996, now U.S. Patent 5,817,515, which discloses that anti-α_d antibodies modulate TNF levels in immune complex-induced alveolitis (Column 61, lines 64-67, of U.S. Pat. 5,817,515). Also, Applicants note the Examiner's objection regarding the formal drawings and will submit final drawings upon notification of allowance.

III. Amendments

Support for the amendment to claims 11 and 12 can be found throughout the specification. For example, page 37, lines 30-32, disclose that α_d forms a heterodimer in association with CD18. Page 41, lines 21-29, of the specification teaches that the α_d/CD18 heterodimer binds to ICAM-R, while page 43, lines 13-21, demonstrates that α_d/CD18 binds VCAM-1. Further support for the amendment is set out in Section IV.A.

IV. Patentability Arguments

A. The Rejection of Claims 11, 12 and 14 under 35 U.S.C. §112, First Paragraph, May Properly be Withdrawn

The Examiner maintains the rejection of claims 11, 12 and 14 under 35 U.S.C. §112, first paragraph, as assertedly not being enabled by the specification for "any α_d specificity as the target of the claimed methods." The Examiner alleges that Applicants have not provided

sufficient functional characteristics of the α_d molecule set out in claims 11(c) and 12(c) to enable the claimed α_d specificity.

Applicants submit that amendment to claims 11 and 12 to recite that said α_d polypeptide retains a biological activity of an α_d polypeptide, wherein the biological activity is binding to at least one α_d binding partner, obviates this rejection. The specification describes several functional interaction of α_d with various binding partners.

For example, the specification describes that the α_d molecule associates with CD18 to form a functional integrin molecule (see Example 8, page 37-38 examples of α_d binding. The specification discloses that CD11a/CD18 binds ICAM-1, while α_d/CD18 does not bind ICAM-1, demonstrating that α_d exhibits unique properties compared to other β_2 integrin alpha subunits. The specification also teaches that α_d/CD18 binds to ICAM-R with 3-5 fold greater affinity than control protein (BSA). Page 42, lines 10-24, of the specification teaches that α_d binds ICAM-R at a domain different from the CD11a binding domain. The specification further discloses, at page 44, lines 7-8, that the α_d polypeptide does not bind to a mutant ICAM-R. Moreover, at page 43, lines 13-21, the specification demonstrates that α_d binds VCAM-1. Thus, α_d is readily identified based on its ability to bind binding partners such as CD18, ICAM-R, or VCAM-1

Additional examples describing α_d binding to its binding partners may be found at, for instance, page 43, lines 7-11; page 43, lines 21-24; and page 158, lines 20-30 which describe the binding of α_d to specific VCAM-1 domains.

As such, Applicants submit that the rejection of claims 11, 12 and 14 under 35 U.S.C. §112, first paragraph, as lacking enablement, may properly be withdrawn.

B. The Rejection of Claim 14 under 35 U.S.C. §112, Second Paragraph, May Properly be Withdrawn

The Examiner rejected claim 14 under 35 U.S.C. §112, second paragraph, for depending from a cancelled claim. Applicants have amended claim 14 to recite appropriate dependency, thereby obviating the rejection.

C. The Rejection of Claims 11, 12 and 14 under 35 U.S.C. §102(b), May Properly be Withdrawn.

The Examiner maintains the rejection of claims 11, 12 and 14 under 35 U.S.C. §102(b) for assertedly being anticipated by the disclosure of Gallatin, which allegedly teaches methods of treating immune or inflammatory responses with antibodies to α_d. In the office action, the Examiner refers to specific disclosure in Gallatin to purportedly support the rejections.

The Examiner cites to the background of Gallatin as well as the description of the invention and the detailed description for evidence that Gallatin discloses use of α_d antibodies to modulate immune or inflammatory response. The Background of Gallatin cited by the Examiner states at column 3, paragraph 2:

> "The significance of β_2 integrin binding activity in human immune and inflammatory responses underscores the necessity to develop a more complete understanding of this class of surface proteins. Identification of yet unknown members of this subfamily, as well as their counterreceptors, and the generation of monoclonal antibodies or other soluble factors which can alter biological activity of the β_2 integrins will provide practical means for therapeutic intervention in β_2 integrin-related immune and inflammatory responses."

This paragraph however addresses the β_2 family in general and makes no specific reference to α_d. The Examiner then cites the Brief Description of the invention (Column 5, paragraph 5) as evidence of disclosure of anti-α_d antibodies that modulate immune function. However, Applicants note that this paragraph indicates that, <u>if</u> α_d is found on macrophages, it <u>may</u> allow for development of therapeutics to several immune diseases, such as multiple sclerosis. The disclosure proceeds to describe cloning a polynucleotide encoding human α_d, but does not confirm its expression on isolated macrophage cells. A worker of ordinary skill reading these disclosures in Gallatin would not recognize that an α_d antibody would bind to macrophages <u>and</u> subsequently modulate TNF-α release.

Additional disclosure in Gallatin does not reflect the Examiner's position. For example, with reference to α_d-specific antibodies, the Brief Description of Gallatin states:

> "Also comprehended by the present invention are polypeptides and other non-peptide molecules which specifically bind to α_d.

> Preferred binding molecules include antibodies (e.g., monoclonal and polyclonal)...Binding molecules are useful for purification of α_d polypeptides and identifying cell types which express α_d. Binding molecules are also useful for modulating (i.e., inhibiting, blocking or stimulating) *in vivo* binding and/or signal transduction activities of α_d." Column 4, lines 28-41.
>
> Further, column 5, paragraph 4 (lines 34-37) of Gallatin states
>
> "As another aspect of the invention, monoclonal or polyclonal antibodies specific for α_d may be employed in immunohistochemical analysis to localize α_d to subcellular compartments or individual cells within tissues."

Neither of these passages associate α_d-specific antibodies with modulating immune responses.

As stated previously, for a reference to anticipate, that single reference must disclose each and every limitation of the claimed invention. MPEP 2131.01 (III) states that to serve as anticipatory art when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill (*emphasis added*). For a reference that is silent about an asserted inherent characteristic, inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 169 F3d 743, 745, (citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 1268, 20 USPQ2d 1746 (Fed. Cir. 1991)). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Id.

The present invention involves methods for specifically inhibiting TNFα activity from macrophages or splenic phagocytes using monoclonal antibodies to integrin α_d. Gallatin neither discloses that α_d is expressed on human macrophages nor suggests any ability of α_d-specific antibodies to modulate TNFα levels on macrophages. Gallatin simply describes a method for producing α_d-specific antibodies and discloses a general use for the β_2 integrin family of antibodies, without giving any particular examples of α_d-specific monoclonal antibodies.

A worker of ordinary skill in the art with knowledge of a newly identified protein could necessarily expect that a monoclonal antibody could eventually be identified that could block binding of this protein to a binding partner. The blockade of ligand binding by an antibody to a transmembrane protein is an extracellular event that a worker of skill might expect to take place given the specificity of an antibody. The modulation of cell migration to a site of inflammation by α_d antibodies and the modulation of intracellular events are two different principles of inflammatory regulation by α_d antibodies that would not be reasonably expected by one of ordinary skill in the art. The present invention is directed to the regulation of an intracellular event, TNFα expression and release, which one of ordinary skill would not necessarily expect when using an antibody to block binding to an extracellular molecule.

For instance, Example 41, pages 151-152 of the specification ,shows that administering anti-α_d monoclonal antibody to an isolated population of cells (splenic phagocytes) decreases TNFα expression. This suggests that there is an intracellular response stimulated by extracellular binding of the α_d monoclonal antibody. This specific signal transduction is not suggested in or predicted by reading Gallatin.

The disclosure of Gallatin gives no indication that the anti-α_d antibodies would act to modulate TNF activity, and it would not have been so recognized by a worker of ordinary skill in the art reading the disclosure of Gallatin. Thus, Applicants submit that the rejection of claims 11, 12 and 14 under 35 U.S.C. § 102(b) should properly be withdrawn.

D. The Rejection of Claims 11, 12 and 14 under Obviousness-type Double Patenting, May Properly Be Withdrawn

The Examiner rejects claims 11, 12 and 14 based on the doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US Patent 6,251,395 and claims 1-9 of US Patent 6,432,404.

Applicant submits that an objection of obviousness-type double patenting of claims 11-14 as unpatentable over U.S. Patent No. 6,251,395 is inappropriate pursuant to 35 U.S.C. § 121. The present application is a divisional application of serial number 09/193,043, now U.S. Patent No. 6,251,395, and was filed based on a restriction requirement in 09/193,043. 35 USC § 121 states, in part:

> A patent issued on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application...if the divisional application is filed before the issuance of the patent on the other application.

The present application was filed on June 26, 2001, the date of issue of 6,251,395, thereby rendering the '395 patent unavailable as a reference against the present application.

Moreover, a proper obviousness-type double patenting rejection must be made by taking into consideration the claims and only the claims in the patent on which the rejection is based. Non-statutory obviousness-type double patenting requires comparison of the application claims and cited patent claims on a claim by claim basis (MPEP 804). The claims of U.S. Patent No. 6,432,404 recite methods for inhibiting macrophage infiltration or locomotor injury in the CNS using antibodies to α_d.

A worker of ordinary skill in the art reviewing the claims of U.S. Patent No. 6,432,404 would not recognize that the subject matter of the claims would embrace the modulation of TNF-α activity, especially when the application claims and cited patent claims are compared on a claim by claim basis. As stated previously, a worker of ordinary skill would not necessarily equate modulation of locomotor injury with modulation of TNF considering other possibilities known in the art, and mentioned previously (see response of Aug. 11, 2003). Administration of α_d-specific antibodies could modulate macrophage infiltration into the brain by a number of different mechanisms, and it would not be at all apparent to a worker of ordinary skill in the art that the patented claims would embrace the modulation of TNF-α activity.

However, in the interest of expediency, Applicants submit that upon notification of allowance of claims 11, 12 and 14 in the above application, Applicants will file a terminal disclaimer with respect to claims 1-9 of U.S. Patent No. 6,432,404.

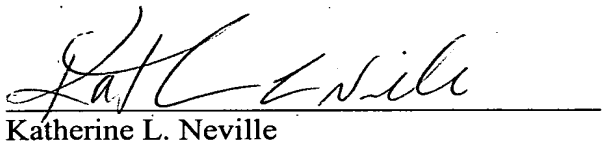
V. Conclusion

In view of the amendments and remarks made herein, Applicants submit that claims 11, 12 and 14 are in condition for allowance and respectfully request expedited notification of the same.

In conjunction with submission of this paper, Applicant submits herewith a Petition for Three-Month Extension of Time and a check in the amount of $1,020 pursuant to 37 CFR 1.17 (a). In the event any additional fees are due, the Assistant Commissioner is hereby authorized to deduct any additional fees from Marshall, Gerstein and Borun, LLP account number 13-2855.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6357
(312) 474-6300

By: 

Katherine L. Neville
Reg. No: 53,379
Agent for Applicants

December 29, 2004